REMARKS

Finality of the Office Action

Applicant respectfully submits that the finality of the Office Action is improper for two reasons. First, the Office stated that the claim rejections under 35 U.S.C. § 112, first paragraph, for lack of enablement are maintained "for the same reasons set forth in the previous Office Action mailed 3/13/07." Office Action, page 3 (emphasis added). The main argument set forth in the previous Office Action was based on the Office's assertion that "[i]t is clear from Applicant example that the starting material (i.e. mesenchymal stem cells) do not express alpha 10 integrin on the cell surface (see Fig.4)." Office Action, mailed 3/13/07, page 4. However, in the currently pending Office Action the Office acknowledged that it had misrepresented the data shown in Figure 4 ("Applicant submits that there is no scientific basis for the Office's contention that the cells in the control (Figure 4a) are different from the cells in the analyzed sample (Figure 4b) with respect to integrin α10 expression. The Examiner agrees with applicant statement" Office Action, page 4). Therefore, Applicant respectfully submits that it is improper to maintain the rejections for lack of enablement for the same reasons set forth in the previous Office Action.

Second, the Office presented new arguments to support the claim rejections under 35 U.S.C. § 112, first paragraph, that were not previously presented and that were not necessitated by Applicant's amendment submitted on August 7, 2007. For example, the Office now contends that the data shown in Figure 4 do not support integrin alpha10 as a marker of mesenchymal stem cells because the cell population tested was not heterogeneous. Office Action, page 3-4. Other new arguments are

indicated in the remarks below. Applicant respectfully submits that it is improper to make the Office Action final if the rejections are based on new arguments that were not necessitated by Applicant's amendment submitted on August 7, 2007.

Status of the Claims

Claims 1-22 are pending. Claims 5, 7-14 and 16-18 were withdrawn from consideration by the Examiner. Claims 1-4, 6, 15 and 19-22 are under consideration.

Amendment of Claims

Claim 1 was amended to include detection and correlation steps that characterize the method of utilizing an integrin α10 chain or an integrin α10 chain and integrin α11 chain as a marker for mammalian mesenchymal stem cells (MSCs). This amendment finds support throughout the specification, for example, in the abstract, paragraphs 63-84, and the originally filed claims.

Claim 3 was amended to clarify the correlation step that describes how detection of integrin α10 chain or integrin α10 chain and integrin α11 chain expression allows the identification of a mammalian mesenchymal stem cell. This amendment finds support throughout the specification, for example, in paragraphs 75-84 and 125.

Claim 15 was amended to include contacting and correlation steps that characterize the method of utilizing an integrin α10 chain or an integrin α10 chain and integrin α11 chain as a marker for the identification of a mammalian mesenchymal stem cell (MSC). This amendment finds support throughout the specification, for example, in paragraphs 30-37.

None of the amendments added new matter.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-4, 6, 15 and 19-22 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Office Action, page 2. More specifically, claims 1, 3 and 15 were held to be indefinite for lacking a correlation step that describes how the results of the assay allow for the determination. Applicant respectfully traverses. However, in order to expedite prosecution, Applicant has amended claims 1, 3 and 15 to include and/or clarify the correlation steps of the claimed methods.

Furthermore, claim 15 was held to be indefinite for failing to include a contacting step. Applicant respectfully traverses. However, in order to expedite prosecution, Applicant has amended claim 15 by adding a "contacting step". The amended claim includes a contacting step, a detection step, and a correlation step.

In light of the above, Applicant respectfully requests that the rejections under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-4, 6, 15 and 19-22 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. Applicant respectfully traverses for the following reasons.

Heterogeneity of cell populations

The Office argued that using an anti-α10 antibody to identify MSCs in a cell population that was enriched in MSCs by addition of FGF-2 -- as described in Example 3 and demonstrated in Figure 4 -- defeats the purpose of anti-α10 antibodies as

markers of MSCs because the FGF-2 treated cell population contained only MSCs and was therefore not heterogeneous. Office Action, page 3-4. Applicant respectfully disagrees with this argument for the following reasons, and also points out that this is a new argument for rejection that was not presented in the previous Office Action and was not necessitated by Applicant's amendment submitted on August 7, 2007.

First, the cell population tested in Example 3 and shown in Figure 4 was not a homogeneous population of MSCs, as the Office suggested. About 4% of the cells did not express integrin α10 and were therefore not identified as MSCs. Hence, the tested cell population had a certain level of heterogeneity and the use of the anti-α10 antibody allowed to distinguish the MSCs that expressed integrin α10 from other types of cells that did not express integrin α10. As discussed in the response filed on August 7, 2007, a certain level of heterogeneity is generally found in stem cell preparations due to the inherent plasticity of stem cells. In contrast to the Office's assertion, Example 3 and the data in Figure 4 therefore provide conclusive evidence that integrin α10 expression and anti-α10 antibodies are useful as a marker of MSCs in a heterogeneous cell population that "comprises a MSC" as recited in the claims.

Second, in light of the disclosure of the instant application the burden is on the Office to provide evidence that integrin α10 and the anti-α10 antibodies do not work as a marker according to the claims.

FGF-2 effects

The Office further argued that "due to the contradictory activity of the FGF-2, undue experimentation would be required of the skilled artisan to determine the effect of FGF-2 on any particular cell response in view of the instant disclosure." Office Action,

page 5. The Office cites Mudoch et al, Mauney et al, and Bianchi et al to support the contention that FGF-2 activity is "contradictory" and "unpredictable". Office Action, pages 4-5. Applicant respectfully disagrees with this argument for the following reasons, and also points out that this is a new argument for rejection that was not presented in the previous Office Action and was not necessitated by Applicant's amendment submitted on August 7, 2007.

First, Applicant does not understand why a skilled artisan would have to determine the effect of FGF-2 on any particular cell response in order to practice the instant invention. FGF-2 treatment is a tool to maintain and/or enrich MSCs in a heterogeneous cell population, but the use of FGF-2, let alone an understanding of any particular cell response to FGF-2, is not required for use of the instant invention. Hence, the relevance of the Office's argument is unclear.

Second, none of the cited references support the Office's contention that FGF-2 activity is contradictory and unpredictable. Murdoch et al. is entirely consistent with the notion that FGF-2 causes enrichment of MSCs in a heterogeneous bone marrow stromal cell (BMSC) population by acting as a mitogen while maintaining multipotency (see Applicant's reply to the previous Office Action at pages 12-13). The Office acknowledged that Murdoch's enrichment method using FGF-2 "gave a similar result in all different donor samples tested to date." Office Action, page 4 (emphasis added). The Office further acknowledged that Mauney et al show that FGF-2 treatment of MSCs causes the retention of both proliferative capacity and osteogenic differentiation potential. Office Action, page 4. Finally, Bianchi et al reports that "FGF-2 reproducibly increased the proliferation rate in standard BMSC cultures" (Bianchi et al., page 104

(emphasis added)) and that it led to an enrichment of multipotent MSCs. Hence, all of these references are entirely consistent with the notion that FGF-2 reproducibly acts as a mitogen while maintaining the multipotency of MSCs.

Third, the Office acknowledged that "the literature is full of articles that indicate that the addition of FGF-2 to hMSCs is used for the retention of both proliferative capacity and osteogenic differentiation potential in vitro and in vivo." Office Action, page 4. This acknowledgement appears to directly contradict the Office's contention that FGF-2 activity is contradictory and unpredictable.

Integrin α10 expression in MSCs and other cells

The Office further argued that "in order for α10 to be a marker for MSCs, it has to be suitable to distinguish MSCs from chondrocytes, osteoblasts among others since the prior art and the specification indicate that α10 can identify other cells such as chondrocytes []." Office Action, page 5. Applicant respectfully disagrees for the following reasons.

It is demonstrated in Example 1 -- as previously acknowledged by the Examiner -- that integrin α10 is expressed on the surface of human MSCs. It is further known that integrin α10 has a non-ubiquitous, restrictive expression pattern in mammalian tissues. *See, for example, Camper et al., Cell Tissue Res. 306:107-16 (2001).* Integrin α10 protein expression has not been detectable in many of the tissues tested, including testis, liver, spleen or brain. *Id. at 113-114.* Hence, surface-expressed integrin α10 can be used as a marker to distinguish MSCs from all cells that do not express this integrin chain. Applicant's results also revealed that surface-expression of integrin α10 is detectable only on very few cell types besides MSCs, i.e. the expression pattern is

highly restricted. In sum, these data clearly establish that integrin α10 is suitable as a marker for MSCs. A marker -- as understood in the art -- does not require the property of being expressed exclusively in only one particular cell type. If that were a requirement, probably no marker would exist. Rather, a marker requires that its expression is non-ubiquituous and sufficiently restricted to render the marker useful. Integrin α10 certainly fulfills this requirement. Hence, the observation that integrin α10 may be expressed in a limited number of other cell types does not render it unsuitable as a marker for MSCs.

In addition, Applicant points out that this is a new argument for rejection that was not presented in the previous Office Action and was not necessitated by Applicant's amendment submitted on August 7, 2007. Furthermore, it appears to directly oppose the Office's argument in the previous Office Action. There, the Office stated its opinion that "[i]t is not clear that osteogenic, myogenic, marrow stroma, tendogenic/ligamento-genic cells of the hMSC express alpha10 integrin" to support the contention that the claimed method of utilizing integrin α10 as a marker for MSCs can not work because not all MSCs express integrin α10. Office Action, mailed 3/13/07, page 4.

Hence, in the previous Office Action the Office asserted in support of the claim rejections that it is not clear that osteogenic, myogenic, marrow stroma, tendogenic/ligamentogenic cells derived from MSCs (this includes osteoblasts and chondrocytes) express integrin α10. In the oustanding Office Action, the Office asserted in support of the claim rejections that it is clear that some osteogenic, myogenic, marrow stroma, tendogenic/ligamentogenic cells derived from MSCs, namely osteoblasts and chondrocytes, express integrin α10.

This opposing argument further suggests that it was improper to issue a final Office Action, asserting that the rejections for lack of enablement were maintained for the same reasons set forth in the previous Office Action.

Conclusions

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims. If the Examiner believes a telephone conference would be useful in resolving any outstanding issues, the Examiner is invited to call the undersigned at (202) 408-4173.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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By: 
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